

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 April 2001 (19.04.2001)

PCT

(10) International Publication Number
WO 01/27102 A1

(51) International Patent Classification⁷: C07D 401/06,
243/08, A61K 31/4709, 31/551

(21) International Application Number: PCT/EP00/10025

(22) International Filing Date: 11 October 2000 (11.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/416,815 13 October 1999 (13.10.1999) US

(71) Applicant (for all designated States except AT, US): NO-
VARTIS AG [CH/CH]; Schwarzwaldallee 215, CH-4058
Basel (CH).

(71) Applicant (for AT only): NOVARTIS-ERFINDUNGEN
VERWALTUNGSGESELLSCHAFT M.B.H. [AT/AT];
Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): ALBERT, Rainer
[AT/CH]; Wartenbergstrasse 21, CH-4052 Basel (CH).
EHRHARDT, Claus [DE/DE]; Grossmannstrasse 17,
79541 Lörrach (DE). HOMMEL, Ulrich [DE/DE];
Auggenerweg 46, 79379 Müllheim (DE). KALLEN,
Jörg [CH/CH]; Kaltbrunnenstrasse 41, CH-4054 Basel
(CH). MEINGASSNER, Josef, Gottfried [AT/AT]; Max
Margules Weg 10, A-2380 Perchtoldsdorf (AT). ROCHE,

Didier [FR/FR]; 11, rue Henri Ponsier, F-6008 Lyon
(FR). WATTANASIN, Sompong [TH/US]; 11 Divito
Trail, Hopatcong, NJ 07843 (US). WEITZ-SCHMIDT,
Gabriele [DE/DE]; Steinbrecherstrasse 4, 79189 Bad
Krozingen (DE). WELZENBACH, Karl [DE/CH];
Davidsrain 10, CH-4056 Basel (CH).

(74) Agent: BECKER, Konrad; Novartis AG, Corporate
Intellectual Property, Patent & Trademark Department,
CH-4002 Basel (CH).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 01/27102 A1

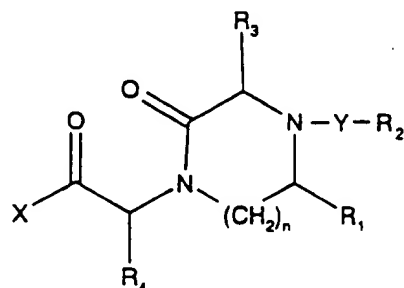
(54) Title: SUBSTITUTED DIAZEPANES

(57) Abstract: The invention provides novel diazepanes having interesting pharmaceutical properties, particularly in preventing or treating disorders or diseases mediated by LFA-1/ICAM-1, -ICAM-2 or -ICAM-3 interactions.

SUBSTITUTED DIAZEPANES

The present invention relates to diazepanes, a process for their production, their use as a pharmaceutical and pharmaceutical preparations containing them.

More particularly the present invention provides a compound of formula I



wherein

n is 1, 2 or 3,

R₁ is H, C₁₋₄alkyl; aryl; or aryl-C₁₋₄alkyl,

Y is C₁₋₄alkylene; -CO-C₁₋₄alkylene; -CO-C₂₋₅alkenylene; -CO-NH-; -CO-C₁₋₃alkylene-NH-; or -CO-O-,

R₂ is an aromatic or heteroaromatic residue, each being optionally substituted by CF₃, halogen, OH, C₁₋₄alkoxy, amino, mono- or di-C₁₋₄alkyl substituted amino, phenyl, benzyl or C₁₋₄alkyl optionally substituted by amino,

R₃ is the side chain present on the C α of an α -amino acid,

R₄ is biphenyl; or benzyl, hydroxy-benzyl, α - or β -naphthyl-methyl, 5,6,7,8-tetrahydro- β -naphthyl-methyl or indolyl-methyl, each being optionally substituted on the ring by CF₃, halogen, OH, C₁₋₄alkoxy, amino, mono- or di-C₁₋₄alkyl substituted amino, phenyl, benzyl or C₁₋₄alkyl optionally substituted by amino, and

X is -CN; -NR₅R₆; or -O-R₈ wherein R₅ is H, C₁₋₆alkyl, aryl or aryl-C₁₋₄alkyl, R₆ is H or C₁₋₆alkyl and R₈ is H, C₁₋₄alkyl, aryl or aryl-C₁₋₄alkyl,

in free form or in salt form.

Alkyl may be linear or branched. When alkyl is substituted by amino, it is preferably monosubstituted, more preferably terminally substituted. Aryl may be e.g. optionally substituted phenyl, naphthyl or dihydro- or tetrahydro-naphthyl. Aryl-C₁₋₄alkyl may be e.g. phenyl-C₁₋₄alkyl, e.g. benzyl, optionally substituted on the ring. Examples of substituents are e.g. halogen, OH, CF₃ or NH₂. Preferably aryl and aryl-C₁₋₄alkyl are unsubstituted.

Halogen may be F, Cl or Br.

When R₂ is an aromatic residue, it may be phenyl, naphthyl, dihydro- or tetrahydro-naphthyl or biphenyl. Suitable heteroaromatic residues as R₂ include e.g. pyridyl, quinolyl, isoquinolyl, dihydro-, tetrahydro-quinolyl or -isoquinolyl, e.g. 1,2,3,4-tetrahydro-quinolyl, benzo-thienyl, indolyl or pyridyl-phenyl. By optionally substituted tetrahydro-quinolyl or indolyl is also meant tetrahydroquinolyl or indolyl wherein the nitrogen is substituted, e.g. by C₁₋₄alkyl, e.g. methyl or ethyl. When substituted, R₂ may be mono- or polysubstituted, e.g. disubstituted.

The α -amino acid or aromatic α -amino acid from which is derived the side chain present on the C α as R₃, may be natural or non natural. Suitable examples as R₃ include e.g. propyl, isopropyl, butyl, isobutyl, 1-methyl-propyl, phenyl, benzyl or aminobutyl.

By optionally ring substituted indolyl as R₄ is also meant indolyl wherein the nitrogen is substituted, e.g. by C₁₋₄alkyl, e.g. methyl or ethyl, or benzyl.

The compounds of formula I may exist in free form or in salt form, e.g. addition salts with e.g. organic or inorganic acids, for example, hydrochloric acid, acetic acid, or salts obtainable when R₈ is H as salts with a base, e.g. alkali salts such as sodium or potassium, or substituted or unsubstituted ammonium salts.

It will be appreciated that the compounds of formula I may exist in the form of optical isomers, racemates or diastereoisomers as well as in the form of cis or trans conformers. For example, the carbon atom bearing the substituent R₃ or R₄, respectively, is asymmetric and may have the D- or L-configuration. For example, the carbon atom bearing R₄ has preferably the D-configuration when R₄ is α -naphthyl-methyl; it preferably has the L-

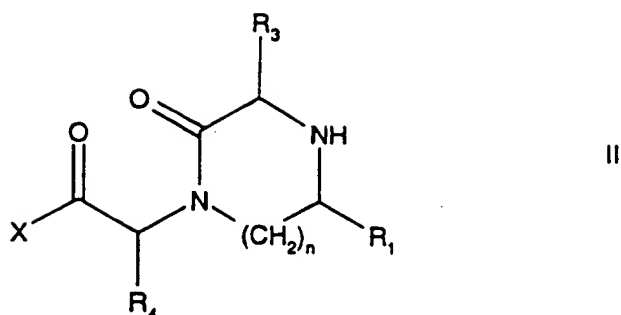
configuration when R_4 is β -naphthyl-methyl. It is to be understood that the present invention embraces all enantiomers and conformers and their mixtures. Similar considerations apply in relation to starting materials exhibiting asymmetric carbon atoms as mentioned above.

In the compounds of formula I, the following significances are preferred individually or in any sub-combination:

1. $n=2$
2. Y is $-\text{CH}_2-$; $-\text{CO}-\text{CH}_2-$; $-\text{CO}-\text{CH}_2-\text{CH}_2-$; $-\text{CO}-\text{NH}-$; $-\text{CO}-\text{CH}_2-\text{NH}-$; or $-\text{CO}-\text{CH}=\text{CH}-$;
3. R_1 is C_{1-4} alkyl, preferably methyl or ethyl, more preferably methyl;
4. R_1 is C_{1-4} alkyl, preferably as indicated, and the carbon atom bearing it has the R-configuration;
5. R_2 is phenyl; phenyl substituted as indicated above, e.g. as indicated in the examples; naphthyl; pyridyl, preferably 2-, 3- or 4-pyridyl; pyridyl-phenyl; quinolyl, isoquinolyl, tetrahydro-quinolyl or substituted quinolyl or isoquinolyl, preferably 2-, 4-, 6- or 8-quinolyl, optionally substituted as indicated above, e.g. as in the examples below;
6. R_2 is quinolyl or isoquinolyl; or substituted quinolyl or isoquinolyl, e.g. by OH, OCH_3 or phenyl; preferably quinolyl;
7. R_3 is isopropyl; n-butyl; isobutyl; or phenyl;
8. R_4 is α - or β -naphthyl-methyl;
9. R_4 is β -naphthyl-methyl and the carbon atom bearing R_4 has the L-(S)-configuration;
10. R_4 is α -naphthyl-methyl and the carbon atom bearing R_4 has the D-(R)-configuration;
11. X is $-\text{NR}_5\text{R}_6$;
12. R_5 is H; C_{1-3} alkyl; or benzyl;
13. R_6 is H or CH_3 , preferably H.

The present invention also includes a process for the production of a compound of formula I, which process comprises appropriately substituting a corresponding compound of formula II as defined below, e.g.:

- a) for the production of a compound of formula I wherein Y is $-\text{CO}-\text{C}_{1-4}$ alkylene or $-\text{CO}-\text{C}_{2-5}$ alkenylene, reacting a compound of formula II



wherein R_1 , R_3 , R_4 , X and n are as defined above,

with a compound of formula IIIa



wherein R_2 is as defined above and Y' is $-CO-C_{1-4}$ alkylene or $-CO-C_{2-5}$ alkenylene or a functional derivative thereof;

- b) for the production of a compound of formula I wherein Y is C_{1-4} alkylene, reacting a compound of formula II above, with a compound of formula IIIb



wherein R_2 is as defined above and Y'' is a direct bond or C_{1-3} alkylene, under reducing conditions;

- c) for the production of a compound of formula I wherein Y is $-CO-NH-$ or $-CO-C_{1-3}$ alkylene- NH ,

reacting a compound of formula II above with a compound of formula IIIc



wherein Y''' is $-CO-NH$ or $-CO-C_{1-3}$ alkylene- NH and each of X_1 and X_2 is a leaving group, e.g. Br, and subsequently reacting the resulting compound with $R_2 - NH_2$; and

- d) for the production of a compound of formula I wherein Y is $-CO-NH-$

reacting a compound of formula II with $R_2-N=C=O$,

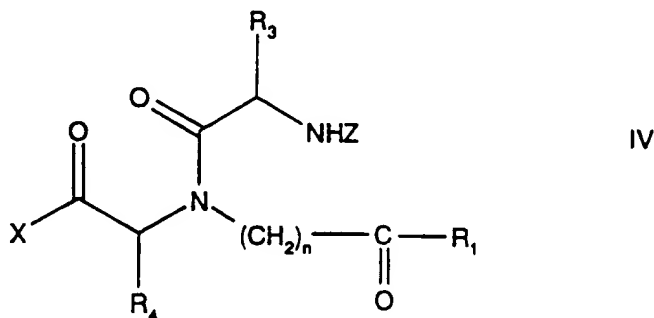
and, where required, converting the resulting compound of formula I obtained in free form to a salt form or vice versa.

A functional derivative of a compound of formula IIIa includes e.g. a halide, ester or anhydride.

Process step a) may be carried out according to known acylation methods, e.g. in liquid phase or in solid phase. The latter case may particularly be suitable for the preparation of a compound of formula I wherein X is NR_5R_6 ; in such a case, the compound of formula II is attached to a resin, e.g. a commercially available resin, e.g. by NH. Once acylation is complete, the desired compound of formula I is cleaved from the resin e.g. by acidic hydrolysis.

Process step b) may be carried out according to known methods, in the presence of a reducing agent, e.g. NaCNBH_3 . Process steps c) and d) may be performed according to known methods.

The compounds of formula II may be produced e.g. by cyclisation of a compound of formula IV



wherein R_1 , R_3 , R_4 , X and n are as defined above and Z is an amino protecting group, in the presence of a reducing agent.

Suitable reducing agents include e.g. NaCNBH_3 , $\text{Na BH}(\text{CH}_3\text{COO})_3$, or Na triacetoxy borohydride. The compounds of formula II may be prepared in liquid or solid phase. In the latter case, the compound of formula IV is attached to a resin by an appropriate group X', e.g. NH. Suitable N-protecting groups may be e.g. as disclosed in "Protective Groups in Organic Synthesis", T.W. Greene, J. Wiley & Sons NY(1981), 219-287, e.g. alcoxycarbonyl such as methoxycarbonyl or t-butyloxycarbonyl, allyloxycarbonyl, arylmethoxycarbonyl such as Fmoc, or benzyloxycarbonyl.

Insofar the production of the starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known in the art or as disclosed hereafter.

The following Examples are illustrative of the invention.

Fmoc = 9-Fluorenyl methoxy carbonyl

Boc = tert.-butoxy-carbonyl

RT = room temperature

THF = tetrahydrofuran

TFA = trifluoroacetic acid

DMF = dimethylformamide

DCCI = dicyclohexylcarbodiimide

EADC = N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride

NMM = N-methyl morpholine

DIPCI = diisopropylcarbodiimide

HOBt = hydroxy benzotriazole

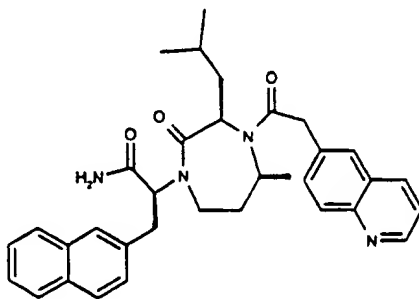
DIPEA = diisopropyl ethyl amine, also called Hünig's base

AcOH = acetic acid

Nal = naphthyl-alanine

Phg = phenyl-glycine

Example 1: (S)-2-[(3S,5R)-3-Isobutyl-5-methyl-2-oxo-4-(quinolin-6-yl-acetyl)-[1,4]diazepan-1-yl]-3-(naphthalen-2-yl)-propionamide

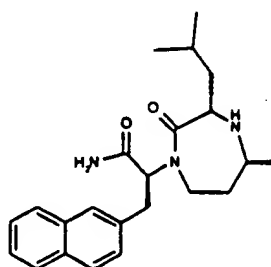


(S)-2-[(3S,5R)-3-isobutyl-5-methyl-2-oxo-[1,4]diazepan-1-yl]-3-(naphthalen-2-yl)-propionamide (382 mg, 1 mmol) is added to a solution of 6-quinolylacetic acid (372 mg, 2 mmol), Hünig's base (170 μ l, 1 mmol) and EADC (383 mg, 2 mmol) in CH_2Cl_2 (50 ml). After 16 hours at RT the reaction mixture is extracted with 0.1N HCl and then with 5% NaHCO_3 solution. Pure title compound is isolated after silica gel chromatography using ethyl acetate --> ethyl acetate/MeOH (9/1) as mobile phase.

MH^+ : 551.4 (ESI)

$\alpha_D^{20} = -12.5^\circ$ ($c = 0.12$ 95% AcOH)

(S)-2-[(3S,5R)-3-isobutyl-5-methyl-2-oxo-[1,4]diazepan-1-yl]-3-(naphthalen-2-yl)-propionamide, used as starting material, may be prepared as follows:



a) N-Boc- β -L-Nal- NH_2 :

DCCI (5.0 g, 24 mmol) is added to a solution of N-Boc- β -L-Nal-OH (6.3 g, 20 mmol), HOBt (3.7 g, 24 mmol) and NH_4OH (25%) (2.0 ml, 24 mmol) in DMF (100 ml) at RT. After 16 hours at RT the solution is filtered and poured into 2 liter 5% aqueous NaHCO_3 solution. The resulting precipitate is filtered off and is dissolved in ethyl acetate (500 ml). After drying over Na_2SO_4 the solvent is removed under reduced pressure. The title compound forms an amorphous solid from c-hexane.

b) H- β -L-Nal- $\text{NH}_2 \cdot \text{HCl}$:

N-Boc- β -L-Nal- NH_2 (6.25 g, 20 mmol) is treated with 60 ml neat TFA at 0°C for 15 minutes. After that the clear solution is poured into 2 l diethylether containing 100 ml of a 3N HCl/diethylether solution. The resulting precipitate is filtered off and is dried at 40°C for 2 hours.

c) N^α -(3-oxo-butyl)- β -L-Nal- NH_2 :

H- β -L-Nal-NH₂.HCl (4.3 g, 17 mmol) is dissolved in 200 ml dioxane at room temperature. After addition of Hünig's base (3.4 ml; 20 mmol) and methylvinylketone (25 ml, 300 mmol) the reaction is kept at room temperature for 16 hours. The reaction is concentrated to 100 ml and the remaining solution is poured into methyl-tert.-butylether (4 l). The precipitate is filtered off, then washed and is used for the next step without further purification.

d) N^α-Boc-Leu-N^α-(3-oxo-butyl)- β -L-Nal-NH₂:

N^α-(3-oxo-butyl)- β -L-Nal-NH₂ (4.5 g, 16 mmol) is added to a solution of Boc-Leu-OH x H₂O (14.8 g, 64 mmol), NMM (3.1 ml, 64 mmol) and DIPC1 (5 ml, 64 mmol) in DMF (100 ml). The reaction is kept at RT for 16 hours, filtered and then poured into 2 liter 5% aqueous NaHCO₃. The aqueous phase is decanted and the sticky residue is dissolved in ethyl acetate and dried over Na₂SO₄. Purification is achieved by silica gel chromatography using ethyl acetate --> ethyl acetate/MeOH (9/1) as mobile phase.

e) H-Leu-N^α-(3-oxo-butyl)- β -L-Nal-NH₂.HCl:

N^α-Boc-Leu-N^α-(3-oxo-butyl)- β -L-Nal-NH₂ (2.9 g, 6 mmol) is treated with 30 ml neat TFA at 0° C for 15 minutes. After that the clear solution is poured into 1 l diethylether containing 50 ml of a 3N HCl/diethylether solution. The resulting precipitate is filtered off and is dried at 40 °C for 2 hours.

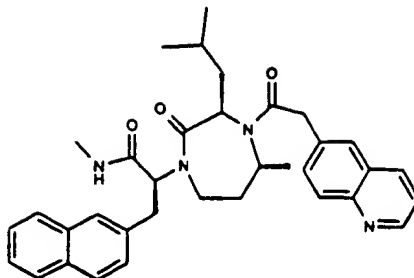
f) (S)-2-[(3S,5R)-3-isobutyl-5-methyl-2-oxo-[1,4]diazepan-1-yl]-3-(naphthalen-2-yl)-propionamide

H-Leu-N^α-(3-oxo-butyl)- β -L-Nal-NH₂.HCl (2.5 g, 6 mmol) is dissolved in dioxane/water (4/1, 100 ml) and the pH is adjusted to 5.4 with 1N aqueous NaOH. The cyclization reaction is carried out with NaCNBH₃ (0.79 g, 12 mmol) at RT. After 30 minutes reaction time most of the dioxane is removed under reduced pressure and the aqueous phase is extracted 3 times with ethyl acetate. Pure endproduct is obtained after silica gel chromatography using ethyl acetate --> ethyl acetate/MeOH (9/1) as mobile phase.

MH⁺: 382.2 (ESI)

α_D^{20} : -46.9 (c=0.18 95% AcOH)

Example 2: (S)-2-[(3S,5R)-3-Isobutyl-5-methyl-2-oxo-4-(quinolin-6-yl-acetyl)-[1,4]diazepan-1-yl]-N-methyl-3-(naphthalen-2-yl)-propionamid

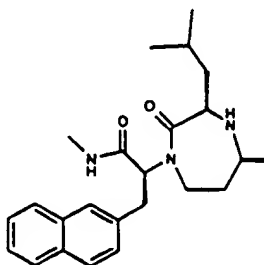


The title compound is obtained by following the procedure of Example 1 and starting with (S)-2-[(3S,5R)-3-isobutyl-5-methyl-2-oxo-[1,4]diazepan-1-yl]-N-methyl-3-(naphthalen-2-yl)-propionamide instead of (S)-2-[(3S,5R)-3-isobutyl-5-methyl-2-oxo-[1,4]diazepan-1-yl]-3-(naphthalen-2-yl)-propionamide.

MH⁺: 565.4 (ESI)

α_D^{20} : +19.9° (c=0.18 95% AcOH)

(S)-2-[(3S,5R)-3-Isobutyl-5-methyl-2-oxo-[1,4]diazepan-1-yl]-N-methyl-3-(naphthalen-2-yl)-propionamide

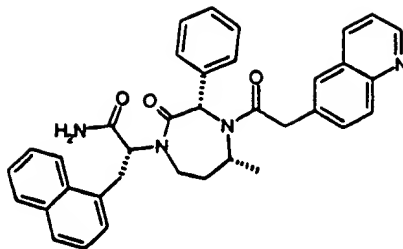


used as starting material may be prepared as disclosed in Example 1, steps (a) to (f) but employing methylamine-hydrochloride (1.4 g, 24 mmol) and NMM (2.6 ml, 24 mmol) instead of NH₄OH (25%) in step a).

MH⁺: 396.0 (ESI)

α_D^{20} : -67.0° (c=0.50 95% AcOH)

Example 3: (R)-2-[(3S,5R)-5-Methyl-2-oxo-3-phenyl-4-(quinolin-6-yl)-acetyl]-[1,4]diazepan-1-yl]-3-(naphthalen-1-yl)-propionamide

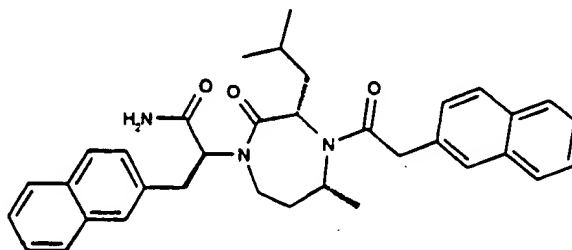


The title compound is prepared by following the procedure of Example 1 but starting from (R)-2-[(3S,5R)-5-methyl-2-oxo-3-phenyl-[1,4]-diazepan-1-yl]-3-(naphthalen-1-yl)-propionamide and using Boc- α -D-Nal-OH in step a) instead of N-Boc- β -L-Nal-OH and Boc-L-Phg-OH in step d) instead of Boc-Leu-OH.

MH⁺: 571 (ES⁺)

α_D^{20} : +187.6 (c=0.15 95% AcOH)

Example 4: (S)-2-[(3S,5R)-3-isobutyl-5-methyl-2-oxo-4-(β -naphthyl-acetyl)-[1,4]diazepan-1-yl]-3-(naphthalen-2-yl)-propionamide



- a) Commercially available Fmoc-Rink-amide MBHA resin (0.61 mmol/g, 1 eq.) is washed with isopropanol (1 x), DMF (2 x), and then treated with a 20% solution of piperidine in DMF (4 x 5 min). The resin is then washed with DMF (1 x), isopropanol (2 x) and DMF (4 x). In a separated vessel, the Fmoc- β -L-Nal-OH (6 eq.) is activated by the sequential addition of a 0.5 M solution of HOBt (6 eq.) in DMF and a 2 M solution of DIPEA (6 eq.). After stirring for 10 min this solution is transferred to the resin. DIPEA (1 eq.) is added to the suspension of resin which is shaken over night at RT. The shaking vessel is then drained and the resin is washed with DMF (4 x), EtOH (2 x), CH₂Cl₂ (3 x), EtOH (2 x), CH₂Cl₂ (3 x) and dried over a N₂ stream. The resulting resin gives a negative result (yellow color) with the bromophenol blue test and the loading

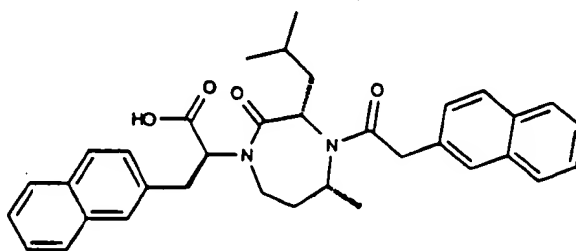
of the resin is controlled by Fmoc titration after treatment of 2-5 mg of resin with 20% piperidine in DMF.

- b) The resin is washed with isopropanol (1 x), DMF (2 x), and then treated with a 20% solution of piperidine in DMF (4 x 5 min). The resin is then washed with DMF (1 x), isopropanol (2 x) and DMF (4 x). A 0.5 M solution of methyl vinylketone in DMF is then added and the resulting suspension is shaken over night at RT. The shaking vessel is then drained and the resin is washed with DMF (4 x), CH₂Cl₂ (3 x), DMF (2 x), CH₂Cl₂ (2 x) and DMF (3 x). The resulting resin gives a positive result (deep blue color) with the bromophenol blue test and is used directly in the next step without drying.
- c) The resin is washed with DMF (2 x). A 0.5 M solution of Fmoc-Leu-OH (10 eq.) in DMF is then added followed by DIPCI (5 eq.). The resulting suspension is shaken for 48 h at RT. The shaking vessel is drained and the resin is washed with DMF (4 x), EtOH (2 x), CH₂Cl₂ (3 x), EtOH (2 x), CH₂Cl₂ (3 x) and is dried over a N₂ stream. Under completion, the resulting resin gives a negative result (yellow color) with the bromophenol blue test. The reaction is re-runned when a positive result (deep blue color) is obtained.
- d) The resin is washed with DMF (1 x) and then treated with a 20% solution of piperidine in DMF (4 x 5 min). The resin is washed with DMF (2 x), CH₂Cl₂ (2 x), DMF (4 x) and then treated with a 0.5 M solution of NaBH₃CN (10 eq.) in 1% AcOH buffered DMF. After over night shaking at RT, the vessel is drained and the resin is washed with 1% AcOH/DMF (4 x), MeOH (4 x), CH₂Cl₂ (3 x), MeOH (3 x), CH₂Cl₂ (4 x) and dried over a N₂ stream. The resulting resin gives a positive result (deep blue color) with the bromophenol blue test.
- e) The resin is washed with DMF (2 x). A 0.4 M pre-mixed solution of β-naphthylacetic acid (10 eq.) and DIPCI (10 eq.) is then added followed by DIPEA (2 eq.). After over night shaking, the vessel is drained and the resin is washed with DMF (4 x), CH₂Cl₂ (3 x), DMF (2 x), CH₂Cl₂ (4 x). The resin is then treated with 50% TFA/CH₂Cl₂ and shaken at RT for 60 min. The resin is washed with 50% TFA/CH₂Cl₂ (1 x), H₂O (2 x), CH₂Cl₂ (3 x) and the filtrate is concentrated using a N₂ stream. The residue is dissolved in a small amount of ethyl acetate and then purified on a short silica gel column using ethyl acetate → ethyl acetate/methanol (1/1) as mobile phase. Fractions containing

the title compound are concentrated and taken then into CH₃CN/H₂O 1/3 and freeze dried to give a white powder.

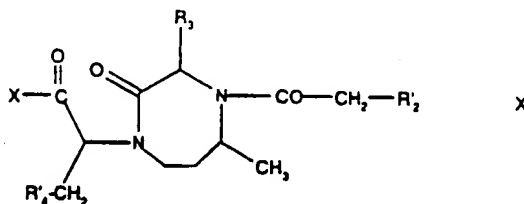
White powder; Rt 18.25 min (HPLC RP C₁₈, 0-100 % CH₃CN in H₂O/20 min); MS *m/z* (relative intensity) (ESI) 533 (100), 550 (73), 572 (10); Anal. Calcd for C₃₅H₃₉N₃O₃: C 76.47, H 7.15, N 7.64; Found: C 76.18, H 7.12, N 7.76.

Example 5: (S)-2-[(3S,5R)-3-isobutyl-5-methyl-2-oxo-4-(β-naphthyl-acetyl)-[1,4]diazepan-1-yl]-3-(naphthalen-2-yl)-propionic acid



This compound is isolated during the purification on silica gel of the compound of Example 4.

The compounds of formula X



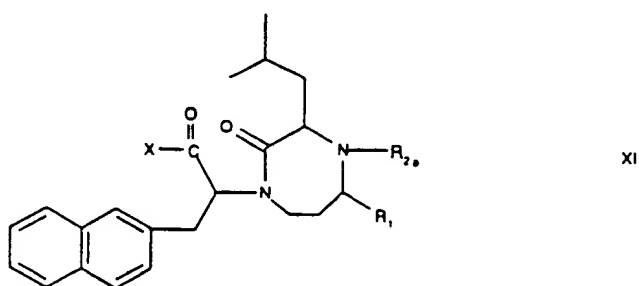
wherein R₂, R₃, R₄ and X are as defined in Table 1 below,
may be prepared by following the procedures of Ex. 1 and 4 and using the appropriate starting materials.

Table 1

Ex	R' ₂	R ₃	R' ₄	X	MH ⁺ (ESI)
6	β-naphthyl	n-butyl	β-naphthyl	NH ₂	550.3
7	phenyl	isobutyl	β-naphthyl	NH ₂	500.3
8	4-pyridyl	isobutyl	β-naphthyl	NH ₂	501.3
9	6-quinolyl	isobutyl	α-naphthyl	NH ₂	551.3
10	3-quinolyl	isobutyl	β-naphthyl	NH ₂	551.3
11	6-quinolyl	isobutyl	β-naphthyl	OCH ₃	566.3
12	6-quinolyl	isobutyl	β-naphthyl	NH-benzyl	641.4
13	β-naphthyl	isobutyl	β-naphthyl	NHCH ₃	564.3
14	4-Bromo-phenyl	isobutyl	β-naphthyl	NH ₂	580.3
15	β-naphthyl	phenyl	α-naphthyl	NH ₂	568.3
16	3-indol-3-yl	isobutyl	β-naphthyl	NH ₂	539.4
17	N-CH ₃ -indol-3-yl	isobutyl	β-naphthyl	NH ₂	553.4
18	p-(3-pyridyl)-phenyl	isobutyl	β-naphthyl	NH ₂	577.4
19	6-quinolyl	isobutyl	5,6,7,8-tetrahydro-β-naphthyl	NH ₂	555.4
20	3,4-dichloro-phenyl	phenyl	α-naphthyl	NH ₂	488.0
21	6-quinolyl	isobutyl	4-bromo-phenyl	NH ₂	579/581
22	p-amino-phenyl-	isobutyl	α-naphthyl	NH ₂	551.3
23	p-(NH ₂ -CH ₂)-phenyl-	isobutyl	α-naphthyl	NH ₂	529.4
24	6-quinolyl	isobutyl	α-naphthyl	NH ₂	551
25	p-[di(CH ₃)-amino]-phenyl	isobutyl	α-naphthyl	NH ₂	543
26	p-chloro-phenyl	isobutyl	α-naphthyl	NHCH ₃	549
27	p-ethoxy-phenyl	isobutyl	α-naphthyl	NHCH ₃	558
28	1-CH ₃ -1,2,3,4-tetrahydro-6-quinolyl	isobutyl	α-naphthyl	NHCH ₃	583
29	3-bromo-5-pyridyl	isobutyl	α-naphthyl	NH ₂	580
30	4-quinolyl	isobutyl	β-naphthyl	NHCH ₃	564
31	7-CH ₃ O-3-quinolyl	isobutyl	β-naphthyl	NHCH ₃	595.4

Ex	R' ₂	R ₃	R' ₄	X	MH ⁺ (ESI)
32	2-phenyl-6-quinolyl	isobutyl	β-naphthyl	NHCH ₃	641
33	1-OH-3-isoquinolyl	isobutyl	β-naphthyl	NHCH ₃	581
34	3,4-di(CH ₃ O)-phenyl	isobutyl	β-naphthyl	NHCH ₃	574
35	3-CH ₃ O-4-OH-phenyl	isobutyl	β-naphthyl	NHCH ₃	560
36	β-naphthyl	phenyl	α-naphthyl	CN	560.3

The compounds of formula XI



wherein R_{2a}, R₁ and X are as defined in Table 2 below,
may be prepared by following the procedures of Ex 1 and 4 and using the corresponding starting materials.

Table 2

Ex	R _{2a}	R ₁	X	MH ⁺ (ESI)
37	4-quinolyl-CH ₂ -CH ₂ -CO-	CH ₃	NH ₂	565.4
38	6-quinolyl-CH ₂ -CO-	CH ₂ CH ₃	NH ₂	565.4
39	4-quinolyl-CH=CH-CO-	CH ₃	NH ₂	563.0
40	4-quinolyl-CH=CH-CO-	CH ₃	NHCH ₃	577.4
41	α-naphthyl-CH=CH-CO-	CH ₃	NHCH ₃	562.2
42	4-pyridyl-CH=CH-CO-	CH ₃	NHCH ₃	513.0
43	benzyl ^a	CH ₃	NHCH ₃	486
44	phenyl-NHCO- ^b	CH ₃	NHCH ₃	515
45	β-naphthyl-NHCO- ^b	CH ₃	NHCH ₃	565
46	(p-F-phenyl)-NH-CH ₂ -CO-	CH ₃	NHCH ₃	547

^a : prepared according to process step b)

^b : prepared according to process step c)

The compounds of Examples 1 to 46 may also be prepared as R- or S-enantiomers or as mixtures as regards the carbon atoms bearing the substituents R₁ (when this is other than H), R₃ and R₄, respectively.

The compounds of formula I, in free form or in pharmaceutically acceptable salt form exhibit valuable pharmacological properties, e.g. inhibiting activity of LFA-1/ICAM-1, -ICAM-2 or -ICAM-3 interactions or inhibiting inflammation, e.g. as indicated in in vitro and in vivo tests and are therefore indicated for therapy.

A. In vitro: Cell Free Assay

The assay measures the binding of soluble human ICAM-1 to immobilized human LFA-1. LFA-1 is purified from JY cells, a human lymphoblastoid B cell-line, by immunoaffinity chromatography as described by Dustin *et al.* (J. Immunol. **148**, 2654-2663, 1992). ICAM-1 mouse C κ fusion protein (ICAM-1) is produced using the baculovirus system as described by Weitz-Schmidt *et al.* (Anal. Biochem. **238**, 184-190, 1996).

Purified LFA-1 is diluted 1:20 in phosphate buffered saline (PBS) containing 2 mM MgCl₂, pH 7.4 and coated onto microtitre plates (Nunc) at 37°C for 3h. Plates are blocked with 1% heat-treated BSA in PBS for 2 hours at 37°C followed by a washing step using PBS, 2mM MgCl₂, 1% fetal calf serum, pH 7.4 (assay buffer). Compounds dissolved at 10 mM in DMSO are diluted in assay buffer and added to the plates. Biotinylated recombinant ICAM-1 in assay buffer (6 µg/ml) is added and allowed to bind at 37°C for one hour. After incubation, wells are washed with assay buffer. Streptavidin-peroxidase diluted 1:5000 in assay buffer is added and incubated for 45 min at 37°C. Plates are then washed with assay buffer and 2,2'-azino-bis(3-ethylbenzothiazoline-6 sulfonic acid) diammonium salt substrate solution is added to each well. The reaction is stopped after 20 min and bound ICAM-1 is determined by measuring the optical density at 405 nm in a microplate reader.

In this assay, compounds of formula I inhibit adhesion of LFA-1 to ICAM-1 with an IC₅₀ ≤ 30 µM, preferably 0.05 to 30 µM. Compounds of Examples 1 and 3 have an IC₅₀ of 0.44 and 0.07 µM, respectively, in this assay.

B. In vivo**i) Murine Thioglycollate Induced Peritonitis**

Thioglycollate is injected i.p. to mice and immediately thereafter the compound to be tested is given s.c. The mice are killed after 4 hours, the peritoneal cavity lavaged and total number of neutrophils in the lavage fluid is determined.

In this assay, the compounds of formula I inhibit thioglycollate induced neutrophil migration when administered p.o. at a dose of from 0.001-50 mg/kg either at the time of thioglycollate injection or 3 hours before.

ii) Allergic Contact Dermatitis (ACD)

Groups of 8 female NMRI mice are sensitized on the shaved abdomen with 50 μ l of oxazolone (Sigma, 2% in acetone) and challenged with 10 μ l of 0.2 or 2.0% oxazolone on the inner surface of the right ear 7 days later. The low concentration of oxazolone for induction of the elicitation phase is used for testing compounds on systemic activity whereas the high concentration is applied for systemic testing. The unchallenged left ears serve as normal controls and dermatitis is evaluated from the individual differences in pinna weight, which is taken as a measure of increase in inflammatory swelling 24 h after the challenge. Dermatitis is evaluated in test- and for comparison in control groups. The test groups are treated with the test compounds either orally (twice, 2 h and immediately before challenge), subcutaneously (immediately before challenge) or topically (30 min after challenge at the site of elicitation of the ACD); the controls are treated similarly with the vehicles alone. For oral and subcutaneous administration the compounds are administered in an oil in water emulsion, for topical administration the compounds are prepared in a mixture of ethanol, acetone and dimethylacetamide. The data of the test- and the vehicle-treated control groups are statistically analysed by ANOVA followed by Dunnet-T-test (normal distribution or data) or by H and U-test, respectively. When administered p.o. at a dose of from 0.1 to 10 mg/kg, compounds of formula I inhibit the elicitation phase of allergic contact dermatitis. Compound of Example 3 has an inhibiting effect in this assay of 40% when administered p.o. at a dose of 2 x 3 mg/kg, or of 50% when applied topically at a dose of 10 mM.

The compounds of formula I are, therefore, useful in the treatment and/or prevention of diseases or disorders mediated by LFA-1/ICAM-1, -ICAM-2 or -ICAM-3 interactions e.g.

ischemia/reperfusion injury e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, acute or chronic rejection of organ or tissue allo- or xenografts, cancer, infection diseases such as septic shock, adult respiratory distress syndrome, or traumatic shock. The compounds of formula I are also useful in the treatment and/or prevention of acute or chronic inflammatory diseases or disorders or autoimmune diseases e.g. rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, diabetes type I and uveitis, asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, cutaneous manifestations of immunologically-mediated disorders or illnesses, inflammatory and hyperproliferative skin diseases (such as psoriasis, atopic dermatitis, alopecia aerata, allergic contact dermatitis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythema multiforme, cutaneous eosinophilias, lupus erythematosus, acne, granuloma annulare, pyoderma gangrenosum, sun burns or toxic epidermal necrolysis), inflammatory bowel disease, Crohn's disease, ulcerative colitis, ophthalmic inflammatory diseases or immune-mediated conditions of the eye, such as autoimmune diseases, e.g. keratoplasty and chronic keratitis, allergic conditions, e.g. vernal conjunctivitis, inflammatory conditions and corneal transplants. For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.1 to about 100 mg/kg body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 500 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form.

For topical use satisfactory results are obtained with local administration of a 1-3 % concentration of active substance several times daily, e.g. 2 to 5 times daily.

The compounds of formula I may be administered systemically or topically, by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets or capsules, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Percutaneous administration via patches or other delivery systems may also be a possible route for prevention or treatment of above diseases.

Pharmaceutical compositions comprising a compound of formula I in free form or in pharmaceutically acceptable salt form in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent. Unit dosage forms for oral administration contain, for example, from about 0.1 mg to about 125 mg of active substance.

Topical administration is e.g. to the skin. A further form of topical administration is to the eye.

The compounds of formula I may be administered in free form or in pharmaceutically acceptable salt form e.g. as indicated above. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

In accordance with the foregoing the present invention further provides:

- 1.1 A method for preventing or treating disorders or diseases mediated by LFA-1/ICAM-1, -ICAM-2 or -ICAM-3 interactions, e.g. such as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;
- 1.2 A method for preventing or treating acute or chronic inflammatory diseases or disorders or autoimmune diseases, e.g. as indicated above, e.g. psoriasis or other inflammatory skin diseases, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;
2. A compound of formula I, in free form or in a pharmaceutically acceptable salt form for use as a pharmaceutical, e.g. in any of the methods as indicated under 1.1 and 1.2 above.
3. A pharmaceutical composition, e.g. for use in any of the methods as in 1.1 and 1.2 above comprising a compound of formula I in free form or pharmaceutically

acceptable salt form in association with a pharmaceutically acceptable diluent or carrier therefor.

4. A compound of formula I or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition for use in any of the method as in 1.1 and 1.2 above.

The compounds of formula I may be administered as the sole active ingredient or together with other drugs in immunomodulating regimens or other anti-inflammatory agents for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders. For example, they may be used in combination with cyclosporins, rapamycins or ascomycins, or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, ABT-281, ASM 981, rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; FTY 720; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine; immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD40, CD45, or CD58 or their ligands; or other immunomodulatory compounds, e.g. CTLA4Ig, or other adhesion molecule inhibitors, e.g. mAbs or low molecular weight inhibitors including Selectin antagonists and VLA-4 antagonists.

Where the compounds of formula I are administered in conjunction with other immunosuppressive / immunomodulatory or anti-inflammatory therapy, e.g. for preventing or treating acute or chronic rejection or inflammatory or autoimmune disorders as hereinabove specified, dosages of the co-administered immunosuppressant, immunomodulatory or anti-inflammatory compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a cyclosporin, on the specific drug employed, on the condition being treated and so forth. In accordance with the foregoing the present invention provides in a yet further aspect:

5. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of formula I in free form or in pharmaceutically acceptable salt form, and a second drug substance, said

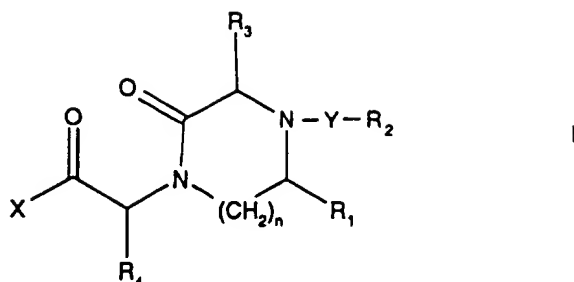
second drug substance being an immunosuppressant, immunomodulatory or anti-inflammatory drug, e.g. as indicated above.

6. A therapeutic combination, e.g. a kit, for use in any method as defined under 1.1 or 1.2 above, comprising a compound of formula I, in free form or in pharmaceutically acceptable salt form, to be used concomitantly or in sequence with at least one pharmaceutical composition comprising an immunosuppressant, immunomodulatory or anti-inflammatory drug. The kit may comprise instructions for its administration.

A preferred compound according to the invention is the compound of Example 3.

CLAIMS

1. A compound of formula I



wherein

n is 1, 2 or 3,

R₁ is H, C₁₋₄alkyl; aryl; or aryl-C₁₋₄alkyl,

Y is C₁₋₄alkylene; -CO-C₁₋₄alkylene; -CO-C₂₋₅alkenylene; -CO-NH-;
-CO-C₁₋₃alkylene-NH-; or -CO-O-,

R₂ is an aromatic or heteroaromatic residue, each being optionally substituted by CF₃, halogen, OH, C₁₋₄alkoxy, amino, mono- or di-C₁₋₄alkyl substituted amino, phenyl, benzyl or C₁₋₄alkyl optionally substituted by amino,

R₃ is the side chain present on the C α of an α -amino acid,

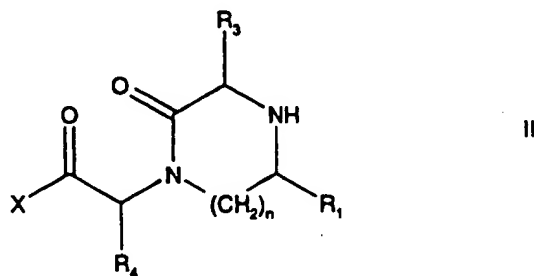
R₄ is biphenyl; or benzyl, hydroxy-benzyl, α - or β -naphthyl-methyl, 5,6,7,8-tetrahydro- β -naphthyl-methyl or indolyl-methyl, each being optionally substituted on the ring by CF₃, halogen, OH, C₁₋₄alkoxy, amino, mono- or di-C₁₋₄alkyl substituted amino, phenyl, benzyl or C₁₋₄alkyl optionally substituted by amino, and

X is -CN; -NR₅R₆; or -O-R₈ wherein R₅ is H, C₁₋₆alkyl, aryl or aryl-C₁₋₄alkyl, R₆ is H or C₁₋₆alkyl and R₈ is H, C₁₋₄alkyl, aryl or aryl-C₁₋₄alkyl,

in free form or in salt form.

2. A compound according to claim 1 wherein n is 2.
3. A compound according to claim 1 wherein R₂ is naphthyl; quinolyl; tetrahydro-quinolyl; tetrahydro-1-methyl-quinolyl; or quinolyl substituted by OH, OCH₃ or phenyl.

4. A compound according to claim 1 wherein R_4 is α - or β -naphthyl-methyl.
5. (R)-2-[(3S,5R)-5-Methyl-2-oxo-3-phenyl-4-(quinolin-6-yl-acetyl)-[1,4]diazepan-1-yl]-3-(naphthalen-1-yl)-propionamide in free form or in salt form.
6. A process for the preparation of a compound of formula I according to claim 1, which process comprises appropriately substituting a corresponding compound of formula II



wherein R_1 , R_3 , R_4 , X and n are as defined in claim 1,

and, where required, converting the resulting compound of formula I obtained in free form into a salt form or vice versa.

7. A compound of formula I according to claim 1, in free form or in a pharmaceutically acceptable salt form, for use as a pharmaceutical.
8. A pharmaceutical composition comprising a compound of formula I according to claim 1 in free form or pharmaceutically acceptable salt form in association with a pharmaceutically acceptable diluent or carrier therefor.
9. A pharmaceutical composition according to claim 8 for use concomitantly or in sequence with a second drug substance, said second drug substance being an immunosuppressant, immunomodulatory or anti-inflammatory drug.
10. A method for preventing or treating disorders or diseases mediated by LFA-1/ICAM-1, -ICAM-2 or -ICAM-3 interactions in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/10025

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/06 C07D243/08 A61K31/4709 A61K31/551

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LAMMEK B ET AL: "BIOLOGICALLY ACTIVE ANALOGUES OF ARGININE VASOPRESSIN CONTAINING CONFORMATIONALLY RESTRICTED DIPEPTIDE FRAGMENTS" JOURNAL OF PEPTIDE RESEARCH, DK, MUNKSGAARD INTERNATIONAL PUBLISHERS, COPENHAGEN, vol. 51, no. 2, 1 February 1998 (1998-02-01), pages 149-154, XP000730043 ISSN: 1397-002X the whole document	1-10
A	T YAMASHITA ET AL: "Synthesis and opiate activity of Pseudo-tetrapeptides" CHEM PHARM BULL, vol. 45, no. 12, 1997, pages 1940-1944, XP000941771 the whole document	1-10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

20 December 2000

Date of mailing of the international search report

10.01.01

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

Inter. ...ional Application No

PCT/EP 00/10025

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	M PIERCY: "Analgesic Activities of Spinal Cord Substance P Antagonists" BRAIN RESEARCH, vol. 385, no. 1, 1986, pages 74-85, XP000945073 See Table III, pages 79-80 -----	1-10
A	EP 0 519 433 A (HOECHST AG) 23 December 1992 (1992-12-23) see compounds of formula III and I, especially the definitions of R1 and R3 -----	1-10
A	EP 0 365 992 A (ABBOTT LAB) 2 May 1990 (1990-05-02) see especially definitions of T and R1 -----	1-10
A	WO 99 20618 A (UPJOHN CO ;GAMMILL RONALD B (US); NUGENT RICHARD ALLEN (US); VANDE) 29 April 1999 (1999-04-29) the whole document -----	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/10025

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. l. Application No

PCT/EP 00/10025

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0519433	A	23-12-1992	BR 9202325 A	19-01-1993
			CA 2071744 A	22-12-1992
			CN 1068112 A	20-01-1993
			CZ 9201906 A	13-01-1993
			FI 922875 A	22-12-1992
			HU 61744 A	01-03-1993
			JP 5186461 A	27-07-1993
			MX 9203070 A	01-12-1992
			NO 922426 A	22-12-1992
			PL 294870 A	08-02-1993
			ZA 9204522 A	24-02-1993
EP 0365992	A	02-05-1990	AU 4849390 A	28-05-1990
			CA 2000929 A	19-04-1990
			DK 70491 A	17-06-1991
			EP 0439556 A	07-08-1991
			JP 4501566 T	19-03-1992
			NZ 231053 A	26-02-1991
			WO 9004917 A	17-05-1990
			US 5153358 A	06-10-1992
			US 5164388 A	17-11-1992
			US 5268476 A	07-12-1993
WO 9920618	A	29-04-1999	AU 1083499 A	10-05-1999